41

1632

PTO/SB/21 (08-03)
Approved for use through 08/30/2003. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/900,715
Filing Date	July 6, 2001
First Named Inventor	Allen
Art Unit	1632
Examiner Name	Joseph T. Woitach
Attorney Docket Number	R-775

Total Number of Pages in This Submission

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☑ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☑ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
- ☐ After Allowance communication to Technology Center (TC)
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) (please Identify below):

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Kelly L. Quast, Reg. No. 52,141
Signature	Kelly L Quast
Date	October 20, 2003

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Typed or printed name	Don Mixon		
Signature	Don Mixon	Date	October 20, 2003

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/900,715	07/06/2001	Keith D. Allen	R-775	3970

7590 07/18/2003

DELTAGEN, INC.
1003 Hamilton Avenue
Menlo Park, CA 94025

EXAMINER
WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Applicants

OIPE JC10 OCT 14 2003 PATENT & TRADEMARK OFFICE

Office Action Summary

Application No.	Applicant(s)
09/900,715	Allen, K.
Examiner	**Art Unit**
Joseph Woitach	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 10, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above, claim(s) *13-15, 24, and 25* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-12 and 16-23* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Jul 6, 2001* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This application filed July 6, 2001, claims benefit to provisional applications 60/216,104, filed July 6, 2000, and 60/223,386, filed August 7, 2000.

Claims 1-25 are pending.

Election/Restriction

Applicant's election with traverse of Group I, claims 1-12, 17-23, in Paper No. 9 is acknowledged. The traversal is on the ground(s) that Applicants argue that Inventions I, II, and III are related to one another and that a separate search or examination would not unduly burden the Examiner. See Applicants election, pages 1-2. This is not found persuasive because Applicants have failed to specifically point out how the inventions are related or why it would not be an undue burden to search and examine each of the three different inventions. As set forth in the restriction requirement, each of Groups I-III are directed to distinct inventions which each have different classes and subclasses. Further, beyond the search of the proper class and subclass in the patent literature and in particular in the non-patent literature a particular search of the text to identify the relevant art for each different inventions is required. To establish burden of search, classification of subject matter is one indication of the burdensome nature of the search involved. The literature searches are particularly relevant for this art and far more important in evaluating burden of search. Clearly the restricted inventions encompass different inventions

from different classes and they do not require one to make or practice the other. The search of the art for one group will not be co-extensive with that of another. Applicants have not set forth any specific reason to why it would not be an undue burden to examine all the inventions together, therefore, because each of groups I-III represent different and separate inventions it would constitute an undue burden to examine three separate inventions in one application.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-25 are pending. Claims 13-15, 24 and 25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9. Claims 1-12 and 17-23 are currently under examination.

Specification

The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). In the instant case, the sequence in Figure 2A is not identified by a sequence identifier, neither in the figure nor figure legend (page 8, lines 27-30).

Appropriate correction is required.

The absence of proper sequence listing for this sequence did not preclude the examination on the merits however, **for a complete response to this office action, applicant must submit the required material for sequence compliance.**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a transgenic mouse comprising a disruption of the nucleotide sequence set forth in SEQ ID NO: 1 by homologous recombination with said targeting construct, wherein the mouse exhibits a phenotype of a stimulus processing deficit, an abnormal startle response and a decreased prepulse inhibition, cells obtained from same transgenic mouse, and methods of screening agents using the same transgenic mouse, does not reasonably provide enablement for all other transgenic non-human animals, cells obtained from the same, and methods of using the same comprising a disruption in a protein phosphatase 2C (PP2C) gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The basis of the instant rejection focuses on two related issues: (1) the failure of the instant disclosure to provide adequate guidance to make a targeting construct with any other sequence besides the EST set forth in SEQ ID NO: 1; and (2) the use of said targeting vectors to generate and use any knock-out non-human animal or cell in which the endogenous protein phosphatase 2 C (PP2C) gene is simply disrupted without providing a useful phenotype. The claims are directed to making and using any non-human transgenic animal with a disruption in

the PP2C gene, and encompasses making separate and individual targeting vectors for each non-human animal encompassed by the claims. The claims are broad encompassing any non-human animal, and thus the specific endogenous PP2C sequences of any non-human animal.

The specification teaches the partial coding region of a single mouse sequence which has been termed and asserted to be a PP2C encoding sequence, which is specifically set forth as SEQ ID NO: 1. SEQ ID NO: 1 was known in the art at the time of filing, and by homology comparisons has been indicated to be a putative PP2C coding region (see AF117832 Genbank entry deposited March1999). Moreover, while the specification terms SEQ ID NO: 1 as a PP2C gene, it does acknowledge that SEQ ID NO: 1 is AF117832 and that it is "a *partial* murine cDNA sequence (501 bases) for a *putative* PP2C mRNA" (*emphasis added*, page 2, lines 14-17). The specification provides no other specific information on how the sequence was derived or any further information on the complete coding region or characterization of even the encoded partial protein. The only specific information for the sequence disclosed is present in the Genebank entry that indicates that it was obtained from a cDNA library with *degenerative* oligonucleotides (see title information). Additional homology comparisons with mRNA sequences encoding the complete protein previously taught in the art indicate that SEQ ID NO: 1 may encode a protein related to a PP2C protein, however it does not share identity with the full sequence previously identified as murine PP2C (see U09218 Genbank entry deposited October 1994).

The basis of the instant rejection focuses on the breadth of the instant claims, in particular two points: 1) the failure of the instant specification or the art of record to provide a nexus

between disruption of any of PP2C gene sequence and providing a transgenic animal which demonstrates a stimulus processing deficit or abnormal startle response combined with the failure of the specification to teach how to use any other transgenic animal with a disruption in the PP2C gene which does not result a stimulus processing deficit or abnormal startle response; and 2) the ability to make and practice the claimed invention in species other than mice because of the reliance of knockout technology on embryonic stem cells. Claims 17-23 are included in the basis of the rejection because though particular claims may encompass an enabled embodiment of one of the points set forth above, the claims still encompass the embodiments of the other two points, therefore are still subject to the limitations of the remaining points. (It is noted that claims 1-12 are not included in the basis of the rejection because they do not specifically require a particular resulting phenotype to make, use or practice).

Many types of protein phosphatases are known in the art and generally 'are implicated in the molecular mechanism by which extracellular signals regulate extracellular functions' (Klump *et al.* page 328, bridging first and second columns). Protein phosphatases are classified into families by specific biochemical criteria where PP2C members are classified by their dependence on Mg2+ (Klump *et al.* page 328, middle of second column). Protein phosphatase 2 C expression and activity of various isozymes has been characterized in detail for its role in various animal tissues. For example, Travis *et al.* teach that protein phosphatase 2 C can dephosphorylate cystic fibrosis transmembrane conductance regulator (CFTR). While Travis *et al.* teach that experimental evidence indicates that protein phosphatase 2 C is implicated in CFTR

control, the importance of 'PP2C in regulating CFTR appears to differ among tissues' and 'may reflect differential localization or regulation of the phosphatases in different cell types' (page 11059, second column). Travis *et al.* conclude 'that little knowledge of how the activity of PP2C is governed' and suggest the need to identify the molecular basis for PP2C regulation (page 11059, bottom of second column). Klumpp *et al.* provide similar conclusions for the need to further characterize the various isozymes PP2C (page 337, bottom of second column). However, the conclusion of Klumpp *et al.* is based on studies for the role of PP2C in the retinae (page 328, see summary in abstract). Both Travis *et al.* and Klumpp *et al.* provide evidence for the complicated role of PP2C in signal transduction and its role in a wide variety of tissues *in vivo*. As noted above, the sequence disclosed as SEQ ID NO: 1 in the instant specification is a putative PP2C sequence. The specification silent with respect to any guidance to what isozyme the putative PP2C sequence may represent and provides no characterization of the expression or role of the putative PP2C sequence *in vitro* or in any animal. Examiner acknowledges that disrupting the endogenous gene represented by SEQ ID NO: 1 in the genome of a transgenic knock-out mouse results in an unexpected phenotype of a stimulus processing deficit, an abnormal startle response and a decreased prepulse inhibition. However, in light of the complicated and diverse role of other PP2C isozymes described in the art, in particular PP2C's role in tissues not associated with the brain, it is not clear that disrupting other PP2C isozymes known and described in the art would result in the phenotype recited and required by the instant claims. Even with respect to the particular phenotype of startle response as measured by

prepulse inhibition Paylor *et al.* teach that phenotype may vary among various mouse lines commonly used in the laboratory (page 169, see summary in abstract). Further, Paylor *et al.* teach that each of the phenotypes characterized are not correlative of each other, indicating that the different responses are due to different genetic components (top of page 178). In summary, in light of the diverse and complex role of PP2C isozymes known and described in the art, the specification fails to provide a nexus between the affects of disrupting the gene represented by SEQ ID NO:1 with any other PP2C known in the art.

Moreover, the art of transgenics is not a predictable art with respect to transgene behavior. Without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species. This observation is specifically supported by Hammer *et al.* who report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277). Specifically, the same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. With respect to the specific phenotype described in the instant specification, as noted above Paylor *et al.* teach that phenotypes may vary even among various mouse lines (page 169, see summary in abstract). This is also supported among mammals in general by Wall *et al.* (J. Dairy Sci) who report that "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies." (see page 2215, first paragraph). With respect to generating knock-out mice with predicted phenotypes

Nishi *et al.* (EMBO) teach that while nociceptin had been implicated in a variety of physiological functions (page 1858, middle of second column), disruption of the endogenous gene in transgenic mice did not result in an observable phenotype related to previously described functions. Given species differences in the expression of a transgenes, and one of skill in the art would have been required to undergo undue experimentation to determine which transgene constructs would produce the desired phenotype in all animals encompassed by the claims. Furthermore, given the complex and diverse role of the PP2C family throughout the animal there is little expectation that what may be observed in altering one gene would correlate to the same change in altering a different isozyme of that gene. Finally, given the diversity of the resulting phenotype even among mouse strains, there would be little expectation that models generated in mice would necessarily extend to other animals. Absent of evidence to the contrary, it is not clear that the knock-out constructs represented by SEQ ID NO: 1 would be functional in any other species or extend to other known PP2C genes.

Finally, the instantly claimed methods are drawn to the use of embryonic stem cells for the introduction of a disruption into the endogenous PP2C gene. Beyond the specific target sequence construct the specification provides only general guidance for the generation of a transgenic mouse through the use of knock-out technology. The basis of this portion of the rejection focuses on the failure of the instant specification and the art to teach embryonic stem cells for the generation of a transgenic animal other than that for the mouse. The specification provides guidance for the use of methodology known in the art for introducing a disruption

through homologous recombination and for the generation of a transgenic animal relies on the use of embryonic stem cells. Currently, however, only totipotent embryonic stem cells for the mouse capable of giving rise to an animal with a transgene present in the somatic cells and the germ cells are available (reviewed in Seamark and Moreadith *et al.*). There is no guidance in the instant specification, nor the art of record, which would support the breadth of the instantly claimed methods for generating transgenic animals through the use of embryonic stem cells from animals other than the mouse. The instant application has demonstrated the generation of transgenic mice with a disruption in a putative PP2C gene sequence with methods known in the art, however, neither the instant specification, nor the art of record, has resolved the many complexities of obtaining or generating totipotent embryonic stem cells for use in the instantly claimed methods. While the steps in the methodology to create transgenic mice is routine, the creation of any transgenic animal is not. In particular, no ES cell for animals other than mice exists to date, so the creation of animals which depend on homologous recombination are not enabled in the art. Further, while methods for the introduction of a gene are routine, the expression of the gene and resulting phenotype of the animal is not. Without an actual reduction to practice, it is possible to predict that introduction of a transgene or an alteration to a gene would result a predictable or useful phenotype.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claims 11 and 12 are unclear and confusing in the final step (c) because a non-human transgenic animal with a disruption in the protein phosphatase 2C gene disrupts the expression of the gene and the function of the encoded protein. The final step (c) is unclear in what expression or function will be determined since the protein phosphatase 2C gene is disrupted. Moreover, the claims are confusing because the agents are tested in an assay on a transgenic animal which would appear to yield no outcome because of the gene disruption.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi *et al.* (US Patent 5,464,764) and Hou *et al.* (Biochem Mol Biol Int 32(4)773-380, 1994).

Capecchi *et al.* teach positive-negative selection methods and vectors for use in knock-out technology. Specifically, Capecchi *et al.* teach that any gene of interest can be disrupted by generating a targeting construct wherein two separate sequences homologous to a gene of interest comprise between them a positive selection marker (claims 1-4)(see diagram of figure 1 for construct). Capecchi *et al.* teach that by inserting the targeting construct into a cell and selecting for cells which underwent homologous recombination, one can obtain a cell with a disrupted gene of interest (claim 5)(see figure 2 for mechanism and summary of the prior art column 2, line 35 through column 4, line 9). In particular, Capecchi *et al.* teach that such constructs can be used to disrupt a gene of interest in mouse embryonic stem cells, and from the mouse embryonic stem cells a transgenic animal can be generated to study the *in vivo* physiology of the disrupted gene (column 12, line 58 through column 13, line 11) and provide a working example in mouse ES cells for the generation of transgenic mice (Examples 1-3)(claims 6-9). More specifically, Capecchi *et al.* set forth each of the necessary steps for generating transgenic mice which are homozygous for the disruption starting from embryonic stem cells (column 24, lines 9-48) (claim 10). Capecchi *et al.* teach that any gene of interest can be targeted for disruption by the described vectors and methods, and reduce to practice several targeted genes in mouse ES cells, however Capecchi *et al.* does not specifically teach to target the protein phosphatase 2C gene. At the time of filing several PP2C gene sequences were known and characterized. Hou *et al.* teach the sequences of two isoforms of PP2C isolated from mouse testis (figure 1). Hou *et al.* teach the expression pattern of the isoforms vary among tissues tested and it demonstrated the highest

expression in the testis (see figure 3). Hou *et al.* report that a total of four different PP2C isoforms have been isolated described, and propose that from sequence homology that the isoforms represent different splice variants possibly expressed by different promoters in the various tissues tested (top of page 778 and summary in figure 2). Since Hou *et al.* describe that PP2C sequences which may be differentially spliced and regulated in different tissues *in vivo*, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the methods described by Capecchi *et al.* to generate a transgenic mouse in which the PP2C sequence was disrupted in the proposed intron sequences to determine whether a single PP2C gene generates the various isoforms as hypothesized by Hou *et al.* One having ordinary skill in the art would have been motivated to use the knock out methodology of Capecchi *et al.* to directly test the observations and hypothesis of Hou *et al.*, and to further determine the physiological affect of modifying the ability of the various isoforms to be generated in a transgenic mouse. Because the expression patterns of the various isoforms was described by Hou *et al.* one of skill in the art would have been motivated to determine the physiological affect of altering the expression pattern among the tissues tested to better characterize the function of the various isoforms in each of the tested tissues. There would have been a reasonable expectation of success to use the knockout methods described by Capecchi *et al.* for any gene of interest in light of the success with the various genes of interest reduced to practice, in order to target the PP2C gene for disruption with the sequences disclosed and partially characterized by Hou *et al.*

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Tong *et al.* (JBC 25:35282-35290, 1998) teach additional mammalian PP2C isozyme sequences known at the time of filing. Tong *et al.* provide a characterization of the PP2C gene and provide evidence for a role in the regulation of cell cycle control.

Hardie (Soc Exp Biol, 1990) provides and overview for the divergent functions and roles of PP2 molecules known in the art.

Genebank U09218 (MMU09218) (May 1994) mouse serine/threonine phosphatase 2C sequence isolated from the testis.

Genebank AA498729 partial mouse EST sequence isolated from a pooled organ library derived from a 7 day old DVB/N mouse (July 1997).

Conclusion

No claim is allowed.

Claims 11, 12 and 17-23 are free of the art of record. In particular, various PP2C sequences were known and characterized at the time of filing, and from the characterization of these PP2C genes there was no suggestion that a disruption in a PP2C gene in a transgenic

animal would result in the phenotype of a stimulus processing deficit and abnormal startle response as set forth in the claims. Further, it is noted that the sequence set forth in Genebank AF117832 is the same as reduced to practice in the instant disclosure, however the sequence represents a putative PP2C polynucleotide sequence and because of the unpredictability of the art of transgenics there would have been no motivation to disrupt a gene represented only by a partial EST of a putative gene sequence or the expectation of success for any predicative or useful phenotype in a resulting transgenic animal. Finally, it is noted that a stimulus processing deficit and abnormal startle response are phenotypes observed in patients with schizophrenia thus, transgenic animals demonstrating these phenotypes could serve as models for future drug discovery. However, while claims 17-23 are free and not obvious over the art of record, the claims are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

Joe Woitach

AU 1632